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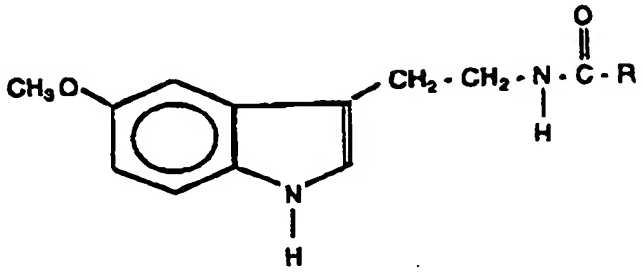
(54) **Title:** MELATONIN DERIVATIVES AND THEIR USE IN COSMETIC OR DERMOPHARMACEUTICAL COMPOSITIONS

(57) **Abstract:**

The invention discloses the synthesis and use of novel lipophilic melatonin homologues of general formula (a) in which R = a C11 to C19 alkyl chain, linear or branched, saturated or unsaturate, hydroxylated or not. These derivatives are preferably obtained by 5-methoxy-trypternin acylation. They are designed for use in cosmetic or dermopharmaceutical compositions for hydrating, regenerating, anti-seborrheic, anti-wrinkle bleaching skin treatment and for the prevention of actinic damage caused by the sun and by the atmosphere.



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The skin is the body's largest organ, but also the one which is most exposed to diverse stresses: irritations due to the environment (pollution, allergies), bad weather (wind, rain, cold, solar radiation, drying), and physical treatments (shaving, depilation, rubbing, shocks). The skin responds to these stresses by its defense mechanisms, which are the thickening of the epidermis, enzymatic defense systems (SOD, catalase, peroxidases), the inflammatory and/or immune response, and seborrheic secretions.

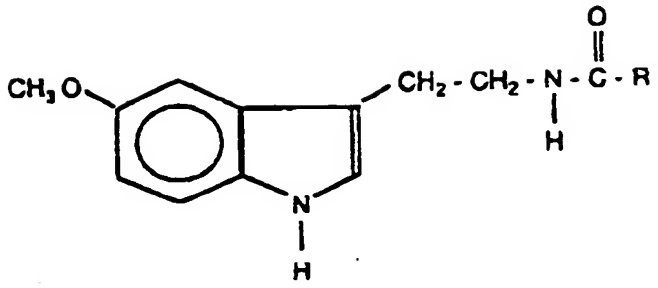
Helping the skin in this task is the goal of modern cosmetology and dermopharmacology. These disciplines accomplish this by contributing molecules or substances which stimulate, protect, nourish, and repair the skin.

The molecule called melatonin (5-methoxy-N-acetyl tryptamine) is naturally produced in the pineal gland and possesses a large number of biological properties. Essentially, it intervenes in the regulatory processes of the circadian rhythm, but numerous systemic activities have been described.

Its dermatological or cosmetic use has been proposed in a certain number of patents:

The patents JP 61221104 (Shiseido) and EP 438856 (Shiseido) claim the use of melatonin to protect the skin against UV radiation and the resulting actinic aging, the patent JP 61212512 (Shiseido) describes the use of melatonin as a hair growth stimulator. Technically, this substance poses the problem of cutaneous absorption: melatonin is not very soluble in common cosmetic or dermopharmaceutical carriers. The patents WO 95/02404 and WO 87/00432 describe systems of transdermal administration which use a controlled delivery technology in an attempt to remedy the problem of solubility and diffusion.

The discovery which represents the subject of this patent is the fact that melatonin homologs carrying an N-acyl group having a long fatty chain in place of the N-acetyl group possess greater affinity for the skin and make it possible to penetrate more easily into the epidermal or dermal layers. These substances can then be enzymatically deacylated in the skin to liberate 5-methoxy tryptamine (5-MT), which is the precursor of melatonin, but which itself is also an active molecule. The derived objects of this patent correspond to the general formula:



where R = a C11 to C19 alkyl chain, which can be straight-chain or branched, saturated or unsaturated, and hydroxylated or unhydroxylated.

Such molecules are synthesized from 5-methoxytryptamine, and they are attached to the acyl chain using methods known for mixed anhydrides, activated esters, acid chlorides, and other amide coupling activators.

By way of example, we describe the synthesis of N-palmitoyl-5-methoxytryptamine:

A 250 ml reactor equipped with a cooler, a temperature probe, an agitator, a pouring funnel, and an argon input, has 9.5 g of 5-methoxytryptamine and 200 ml of tetrahydrofuran (THF) introduced into it. 14.4 g of palmitoyl chloride are poured in at a temperature between -5° C and +5° C over 10 minutes, and then 5.3 g of triethylamine are poured in at a temperature between -5° C and +5° C over 5 minutes.

After the reaction goes to completion (monitored by TLC), the mixture is allowed to return to room temperature, and the suspension is filtered; the filtrate is concentrated and recrystallized in 140 ml of toluene. After washing and drying, 16.9 g of a white powder is obtained: N-palmitoyl-5-methoxytryptamine (yield 79%), m.p. 99-100° C, Rf value (on Merck plate 1.05554, ethyl acetate): 0.70, single task at UV 254 nm.

The C, H, N, IR, and NMR analyses confirm the structure of the product obtained. The same procedure is used to prepare the derivatives N-lauroyl, N-myristoyl, N-stearoyl, N-eicosanoyl, N-docosanoyl, N-palmitoleoyl, N-oleoyl, N-linoleoyl, N-linolenoyl and N-arachidonyl, N-aleuretoyl (9,10,16-trihydroxypalmitoyl) of 6-methoxytryptamine.

These molecules are more easily incorporated into cosmetic products; they can be emulsified, dissolved in solubilizing carriers (glycols, polyhydric alcohols, polyethoxylated solvents), included into liposomes. Moreover, these lipophilic derivatives posses a stronger affinity for the epidermis and therefore an increased cosmetic activity.

The following test shows the advantage of the lipophilic structure of the melatonin derivatives:

Example no.1:

[^{125}I]-2-iodomelatonin and [^{125}I]-2-iodo-5-methoxy-N-palmitoyltryptamine are applied in dilute solution to a skin explant, mounted on a Frantz-type diffusion cell. After 30 minutes, 1 hour, 2 hours, and 4 hours, the penetration balance is studied: the top layers of the epidermis are removed by stripping using a self-adhesive, the epidermis is separated from the dermis by a treatment with trypsin and/or caustic soda, and the liquid remaining in the receiving part of the diffusion cells is collected. The quantity of radioactive molecules in each of the fractions is evaluated by scintillation counting after the samples are reduced to ash. The results show that the lipophilic derivative N-palmitoyl-5-methoxytryptamine is concentrated in the epidermis (radioactivity 155 times stronger than for the epidermis treated with melatonin) and in the deeper strippings.

Little radioactivity is found in the dermis and in the remaining liquid. Most of the unmodified melatonin is found in all the first stripping layers, therefore at a level of penetration where the biological activity of the product is not guaranteed.

The melatonin homologs which represent the subject of this patent are therefore particularly well adapted to cosmetic or dermopharmaceutical use with topical application. Moreover, they are not irritants, are well tolerated, stable, and effective.

A non-limiting example is provided by a cream formulated with the derivative of N-lauroyl-5-MT:

Example no.2

Solution of N-lauroyl-5-MT derivative incorporated in a face cream:

Brij® 721 Steareth-21	2.4
Brij® 72 Steareth-2	2.6
Arlamol® E PPG-15 stearyl ether	8.0
Beeswax	0.5
Abil® ZP 2434 stearoxy dimethicone → silicone surfactant	3.0
Propylene glycol	3.0
Carbopol® 941	0.25
Triethanolamine	0.25
N-lauroyl-5-MT (2% in ethoxydiglycol)	7.5
Water, preservatives, perfumes qs	100 g

The cosmetic activity of these derivatives manifests itself by a better appearance of the skin: more hydrated, less wrinkled, clearer and having a homogenous tint, firmer and having better tone, as is shown in the following study:

Example no. 3:

25 female subjects between 32 and 59 years of age applied a cream containing 1.5% of N-palmitoyl-5-MT for 4 weeks onto one part of their faces, and a placebo cream on the other, without knowing this.

The skin was evaluated by clinical examination, by self-evaluation, and by various quantitative methods (sebometry, corneometry, fermometry), which showed a very good tolerance for creams, an improvement of the clinical signs of dry skin, oily skin, and local discolorations. According to the measurements of seborrhea, the secretion of sebum diminished by 27% on the treated side, and remained stable on the placebo side. The skin is better hydrated (+35%) on the treated sites, and firmer (an increase in tone of 31% over -2% for the placebo) over initial values.

The melatonin homologs which represent the subject of this patent can be used in any galenical form commonly used in a cosmetic or dermopharmaceutical formulation: o/w

and w/o emulsions, milks, lotions, gels, pomades, balms, mousses, body lotions, hair lotions, shampoos, soaps, sticks and crayons, sprays, without this list being limiting.

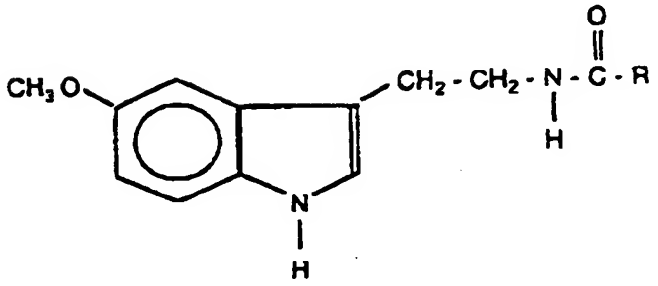
The concentration in which these derivatives are used in the final cosmetic product can vary between 0.0001 and 10% (w/w), preferably between 0.001 and 1%, especially preferably between 0.01 and 0.1% of the weight of the total compound.

The melatonin homologs which represent the subject of this patent can be combined in the cosmetic compounds with any other ingredient commonly used in cosmetics: lipids which are extracted and/or synthesized, gel-forming and viscosifying polymers, surfactants and emulsifiers, water-soluble or lipid-soluble active ingredients, extracts of other plants, tissue extracts, marine extracts.

The melatonin homologs in all their galenical forms (powder, solution, emulsion) can be used in the cosmetic or dermopharmaceutical areas for their anti-wrinkle and anti-aging action, their regulation of seborrhea, their moisturizing and firming action, and protection against the effects of UV radiation. They are beneficial in sensitive-skin products, sun and after-sun creams, face and body products, scalp massage lotions, and aging-prevention products.

CLAIMS

1) Synthetic melatonin homologs for cosmetic or dermopharmaceutical use having the general formula



where R = a C11 to C19 alkyl chain, which can be straight-chain or branched, saturated or unsaturated, and hydroxylated or unhydroxylated.

2) Synthetic melatonin homologs according to Claim 1, characterized by the fact that they are obtained by acylation of the amine function of 5-methoxytryptamine with fatty acids selected from the following: lauric acid, myristic acid, palmitic acid, stearic acid, eicosanoic acid, docosanoic acid, palmitoleic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, and aleuretic acid.

3) Synthetic melatonin homologs according to Claims 1 and 2, characterized by the fact that the melatonin homolog is preferably N-palmitoyl-5-methoxytryptamine.

4) Cosmetic or dermopharmaceutical compounds characterized by the fact that they contain at least one melatonin homolog according to any of Claims 1 through 3, which have previously been dissolved in solvents which can be used in the cosmetic or dermopharmaceutical areas, such as water, ethanol, propanol or isopropanol, propylene glycol, butylene glycol, glycerine, polyethylene glycol, methyl or ethyl ethers of diglycols, cyclic polyhydric alcohols, ethoxylated or propoxylated diglycols or any mixture of these solvents.

5) Cosmetic or dermopharmaceutical compounds characterized by the fact that they contain at least one melatonin homolog according to any of Claims 1 through 4, which have previously been incorporated into cosmetic vectors such as liposomes, chylomicrons, macro-, micro-, and nanoparticles, as well as macro-, micro-, and nanocapsules, or absorbed onto powdery organic polymers such as talcs, bentonites and other mineral supports.

6) Cosmetic or dermopharmaceutical compounds characterized by the fact that they contain the melatonin homologs according to either of Claims 4 or 5 in concentrations which can range from 0.0001% (w/w) and 10%, preferably between 0.001 and 1% (w/w), and especially between 0.01 and 0.1% of the weight of the total compound.

7) Cosmetic or dermopharmaceutical compounds according to any of Claims 4 through 6 characterized by the fact that they represent any galenical form used in cosmetics or dermopharmaceuticals, namely o/w and w/o emulsions, milks, lotions, gels, pomades, balms, mousses, body lotions, hair lotions, shampoos, soaps, sticks and crayons, and sprays.

8) Cosmetic or dermopharmaceutical compounds according to any of Claims 4 through 7 characterized by the fact that the melatonin homologs according to any of Claims 1

through 3 are combined into finished products with any other ingredient commonly used in cosmetics or dermopharmaceuticals: lipids which are extracted and/or synthesized, gel-forming and viscosifying polymers, surfactants and emulsifiers, water-soluble or lipid-soluble active ingredients, extracts of other plants, tissue extracts, and marine extracts.

9) Uses of the melatonin homologs according to any of Claims 1 through 3 in cosmetic or dermopharmaceutical compounds according to any of Claims 4 through 8 for skin or scalp care, especially for all moisturizing, firming, anti-wrinkle, and anti-seborrheic care.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/16 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 06955 A (PULITZER ITALIANA S.R.L.) 30 April 1992 the whole document ---	1,4-9
X	JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 83, no. 2, - 1994 WASHINGTON US, pages 216-218, XP000422956 R. T. BLICKENSTAFF ET AL: "Potential radioprotective agents. Homologs of melatonin" see table 1 -----	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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10 April 1997	21.04.97

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Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	publication
WO 9206955 A	30-04-92	IT 1243846 B	28-06-94
		AT 111450 T	15-09-94
		AU 8715491 A	20-05-92
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		EP 0553155 A	04-08-93